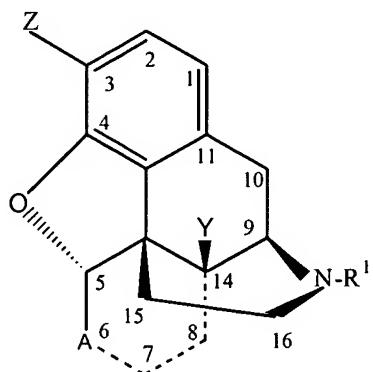


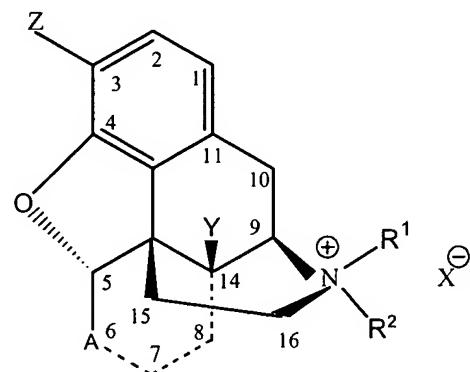
AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A process for the preparation of a quaternary derivative of a tertiary N-substituted morphinan alkaloid, the process comprising contacting a tertiary N-substituted morphinan alkaloid substrate with an alkylating agent in an anhydrous solvent system, wherein the solvent system comprises an aprotic dipolar solvent selected from the group consisting of dimethylacetamide, dimethylformamide, 1-methyl-2-pyrrolidinone, hexamethylphosphoramide, and mixtures thereof with the aprotic dipolar solvent constituting at least 25 wt % of the solvent system, the contacting is carried out within a temperature range of about 55°C to about 85°C, the tertiary N-substituted morphinan alkaloid substrate has the structure of Formula 1 and the quaternary derivative has the structure of Formula 1A: correspond to Formulae 1 and 1A, respectively:



Formula 1



Formula 1A

wherein

A is $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{=CH}_2)-$, $[\text{[-CHA}_1\text{- or -CA}_1\text{=]}] \text{ -CH(A}_1\text{)-, or -C(A}_1\text{)=,}$

A_1 is hydroxy, alkoxy, or acyloxy,

each R is independently hydrocarbyl,

R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl,

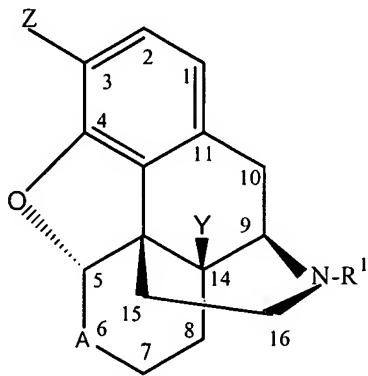
X^\ominus is an anion,

Y , if present, is hydrogen, hydroxy, alkoxy, [[or]] acyloxy, -OTHP, -OSiR₃, -OBn, -OBs, -OTs, or -OMs,

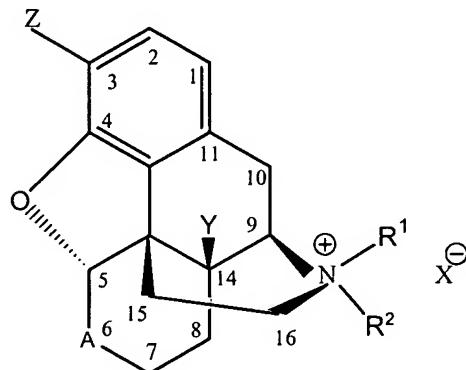
Z is hydroxy, alkoxy, [[or]] acyloxy, -OTHP, -OSiR₃, -OBn, -OBs, -OTs, or -OMs, and

the dashed lines between the carbon atoms at positions 6 and 7, 7 and 8, and 8 and 14, respectively, represent (i) carbon-carbon single bonds, (ii) carbon-carbon single bonds between positions 6 and 7 and between positions 8 and 14, and a double bond between positions 7 and 8, or (iii) conjugated carbon-carbon double bonds between positions 6 and 7 and positions 8 and 14, with the proviso that Y is not present if there is a double bond between the carbons at positions 8 and 14.

2. (Currently amended) The process of claim 1 wherein the tertiary N-substituted morphinan alkaloid substrate is represented by Formula 2 and the quaternary derivative is represented by Formula 2A. correspond to Formulae 2 and 2A, respectively:



Formula 2



Formula 2A

wherein

A is $-C(O)-$, $-C(S)-$, $-C(=CH_2)-$, or [[-CHA₁-]] -CH(A₁)-,

A_1 is hydroxy, alkoxy, or acyloxy,

R¹ is hydrocarbyl or substituted hydrocarbyl,

R² is hydrocarbyl or substituted hydrocarbyl, [[and]]

X[⊖] is an anion,

Y[[,]] is hydrogen, hydroxy, alkoxy, or acyloxy, and

Z is hydroxy, alkoxy, or acyloxy.

3. (Currently amended) The process of claim 2 wherein the tertiary **N-substituted** morphinan alkaloid substrate is naltrexone ((5 $α$)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one), oxymorphone ((5 $α$)-4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one), oxycodone ((5 $α$)-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one), hydromorphone ((5 $α$)-4,5-epoxy-3-hydroxy-17-methylmorphinan-6-one), naloxone ((5 $α$)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one), nalmefene ((5 $α$)-17-(cyclopropylmethyl)-4,5-epoxy-6-methylenemorphinan-3,14-diol) or nalbuphine ((5 $α$)-17-(cyclobutylmethyl)-4,5-epoxymorphinan-3,6,14-triol).

4-5. (Canceled)

6. (Presently pending) The process of claim 1 wherein the alkylating agent is methyl bromide.

7. (Presently pending) The process according to claim 1 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

8-10. (Canceled)

11. (Presently pending) The process according to claim 1 wherein the aprotic dipolar solvent constitutes at least 75 wt. % of the solvent system.

12-14. (Canceled)

15. (Presently pending) The process according to claim 1 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

16-27. (Canceled)

28. (Presently pending) The process according to claim 1 wherein Y and Z are independently -OCH₃, -OAc, -OTHP, -OSiR₃, -OBn, -OBz, -OBs, -OTs, or -OMs wherein each R is independently hydrocarbyl.

29. (Presently pending) The process according to claim 1 wherein said anhydrous solvent system contains less than 0.2 wt. % water and is maintained in a moisture-free atmosphere in a reaction vessel.

30. (Presently pending) The process according to claim 1 wherein said anhydrous solvent system contains less than 0.1 wt. % water.

31. (Presently pending) The process according to claim 1 wherein said anhydrous solvent system contains less than 0.05 wt. % water.

32. (Presently pending) The process according to claim 31 wherein said alkylating agent is a methylating agent.

33. (Canceled)

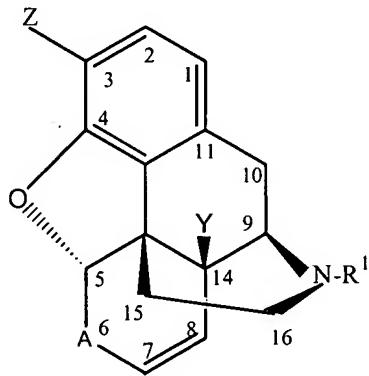
34. (Presently pending) The process according to claim 31 wherein said alkylating agent and said substrate are present in a mole ratio of between 1:1 and 1.5:1, respectively.

35. (Canceled)

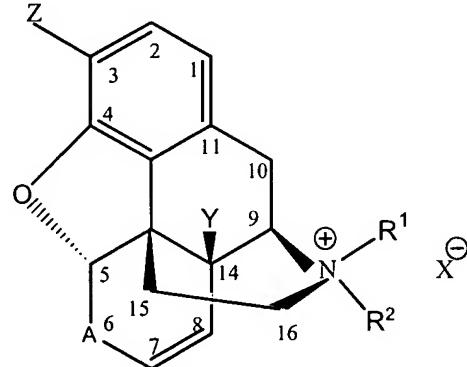
36. (Currently amended) The process according to claim 1 wherein said anhydrous ~~dipolar aprotic solvent~~ system and said substrate are present in a volume-to-weight ratio of 1.5:1 -1.75:1.

37. (Canceled)

38. (Currently amended) The process of claim 1 wherein the tertiary N-substituted morphinan alkaloid substrate is represented by Formula 3 and the product quaternary derivative is represented by Formula 3A. correspond to Formulae 3 and 3A, respectively:



Formula 3



Formula 3A

wherein

A is -C(O)-, -C(S)-, -C(=CH₂)-, or [-CHA₁-] -CH(A₁)-,

A₁ is hydroxy, alkoxy, or acyloxy,

R¹ is hydrocarbyl or substituted hydrocarbyl,

R² is hydrocarbyl or substituted hydrocarbyl, [[and]]

X[⊖] is an anion,

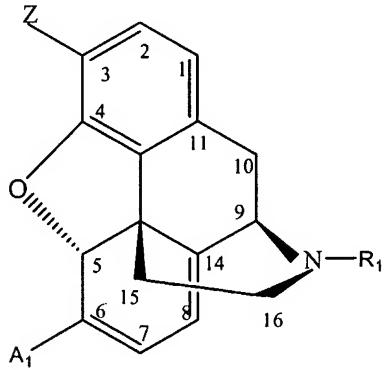
Y[[,]] is [[H]] hydrogen, hydroxy, alkoxy, or acyloxy, and

Z is hydroxy, alkoxy, or acyloxy.

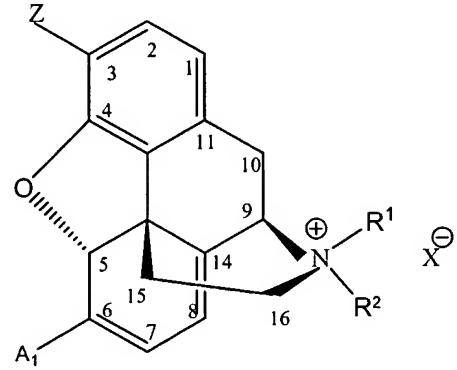
39. (Currently amended) The process of claim 38 wherein the tertiary **N**-substituted morphinan alkaloid substrate is morphine ((5 $α$,6 $α$)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol), codeine ((5 $α$,6 $α$)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol), codeinone ((5 $α$)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one) or 14-hydroxy-codeinone ((5 $α$)-7,8-didehydro-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one).

40-61. (Canceled)

62. (New) The process of claim 1 wherein the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 4 and 4A, respectively:



Formula 4



Formula 4A

A_1 is hydroxy, alkoxy, or acyloxy,

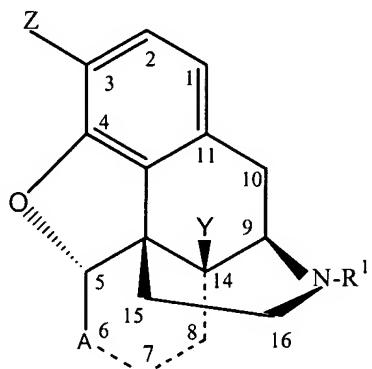
R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl,

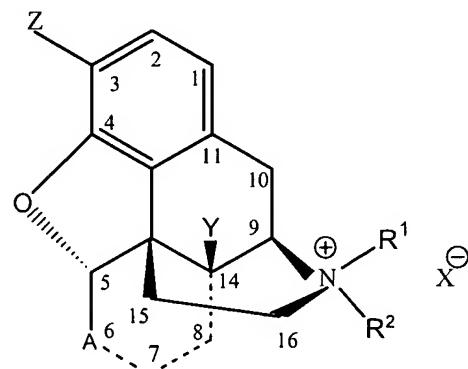
X^\ominus is an anion, and

Z is hydroxy, alkoxy, or acyloxy.

63. (New) A process for the preparation of a quaternary derivative of a tertiary N-substituted morphinan alkaloid, the process comprising contacting a tertiary N-substituted morphinan alkaloid substrate with an alkylating agent in an anhydrous solvent system, wherein the solvent system comprises 1-methyl-2-pyrrolidinone with the 1-methyl-2-pyrrolidinone constituting at least 25 wt % of the solvent system, the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 1 and 1A, respectively:



Formula 1



Formula 1A

A is $-C(O)-$, $-C(S)-$, $-C(=CH_2)-$, $-CH(A_1)-$, or $-C(A_1)=$,

A_1 is hydroxy, alkoxy, or acyloxy,

each R is independently hydrocarbyl,

R^1 is hydrocarbyl or substituted hydrocarbyl,

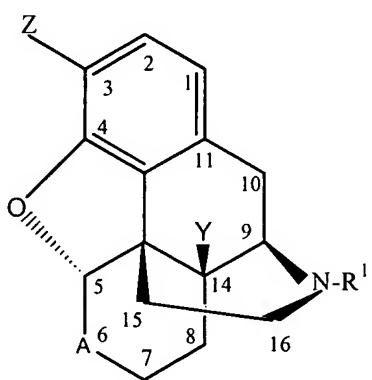
R^2 is hydrocarbyl or substituted hydrocarbyl,

X^\ominus is an anion,

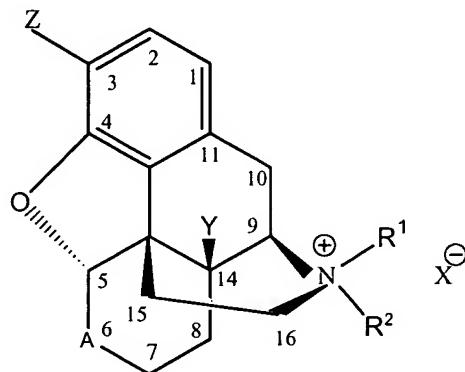
Y , if present, is hydrogen, hydroxy, alkoxy, acyloxy, -OTHP, -OSiR₃, -OBn, -OBs, -OTs, or -OMs,

Z is hydroxy, alkoxy, acyloxy, -OTHP, -OSiR₃, -OBn, -OBs, -OTs, or -OMs, and the dashed lines between the carbon atoms at positions 6 and 7, 7 and 8, and 8 and 14, respectively, represent (i) carbon-carbon single bonds, (ii) carbon-carbon single bonds between positions 6 and 7 and between positions 8 and 14, and a double bond between positions 7 and 8, or (iii) conjugated carbon-carbon double bonds between positions 6 and 7 and positions 8 and 14, with the proviso that Y is not present if there is a double bond between the carbons at positions 8 and 14.

64. (New) The process of claim 63 wherein the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 2 and 2A, respectively:



Formula 2



Formula 2A

A is -C(O)-, -C(S)-, -C(=CH₂)-, or -CH(A₁)-,

A_1 is hydroxy, alkoxy, or acyloxy,

R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl,

X^\ominus is an anion,

Y is hydrogen, hydroxy, alkoxy, or acyloxy, and

Z is hydroxy, alkoxy, or acyloxy.

65. (New) The process of claim 64 wherein the tertiary N-substituted morphinan alkaloid substrate is naltrexone ((5 α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one), oxymorphone ((5 α)-4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one), oxycodone ((5 α)-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one), hydromorphone ((5 α)-4,5-epoxy-3-hydroxy-17-methylmorphinan-6-one), naloxone ((5 α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one), nalmefene ((5 α)-17-(cyclopropylmethyl)-4,5-epoxy-6-methylenemorphinan-3,14-diol) or nalbuphine ((5 α)-17-(cyclobutylmethyl)-4,5-epoxymorphinan-3,6,14-triol).

66. (New) The process of claim 63 wherein the alkylating agent is methyl bromide.

67. (New) The process according to claim 63 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

68. (New) The process according to claim 63 wherein the 1-methyl-2-pyrrolidinone constitutes at least 75 wt. % of the solvent system.

69. (New) The process according to claim 63 wherein Y and Z are independently -OCH₃, -OAc, -OTHP, -OSiR₃, -OBn, -OBz, -OBs, -OTs, or -OMs wherein each R is independently hydrocarbyl.

70. (New) The process according to claim 63 wherein said anhydrous solvent system contains less than 0.2 wt. % water and is maintained in a moisture-free atmosphere in a reaction vessel.

71. (New) The process according to claim 63 wherein said anhydrous solvent system contains less than 0.1 wt. % water.

72. (New) The process according to claim 63 wherein said anhydrous solvent system contains less than 0.05 wt. % water.

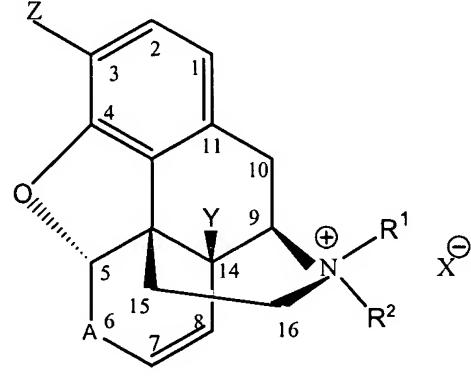
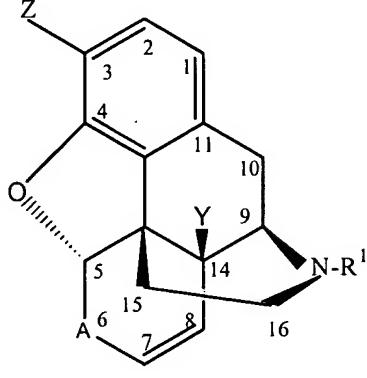
73. (New) The process according to claim 72 wherein said alkylating agent is a methylating agent.

74. (New) The process according to claim 72 wherein said alkylating agent and said substrate are present in a mole ratio of between 1:1 and 1.5:1, respectively.

75. (New) The process according to claim 63 wherein said 1-methyl-2-pyrrolidinone and said substrate are present in a volume-to-weight ratio of 1.5:1-1.75:1.

76. (New) The process according to claim 63 wherein said contacting is carried out within a temperature range of about 55°C to about 85°C.

77. (New) The process of claim 63 wherein the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 3 and 3A, respectively:



Formula 3

Formula 3A

A is -C(O)-, -C(S)-, -C(=CH₂)-, or -CH(A₁)-,

A₁ is hydroxy, alkoxy, or acyloxy,

R¹ is hydrocarbyl or substituted hydrocarbyl,

R² is hydrocarbyl or substituted hydrocarbyl,

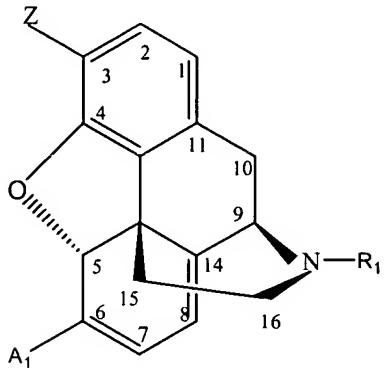
X[⊖] is an anion,

Y is hydrogen, hydroxy, alkoxy, or acyloxy, and

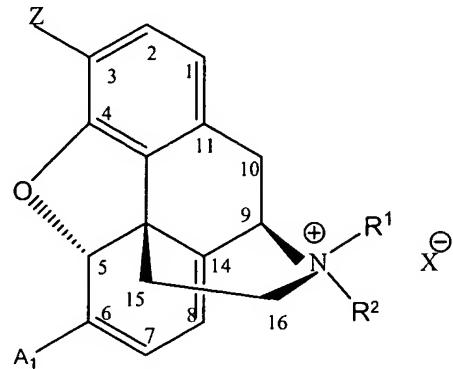
Z is hydroxy, alkoxy, or acyloxy.

78. (New) The process of claim 77 wherein the tertiary N-substituted morphinan alkaloid substrate is morphine ((5 $α$,6 $α$)-7,8-didehydro-4,5-epoxi-17-methylmorphinan-3,6-diol), codeine ((5 $α$,6 $α$)-7,8-didehydro-4,5-epoxi-3-methoxy-17-methylmorphinan-6-ol), codeinone ((5 $α$)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one) or 14-hydroxy-codeinone ((5 $α$)-7,8-didehydro-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one).

79. (New) The process of claim 63 wherein the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 4 and 4A, respectively:



Formula 4



Formula 4A

A₁ is hydroxy, alkoxy, or acyloxy,

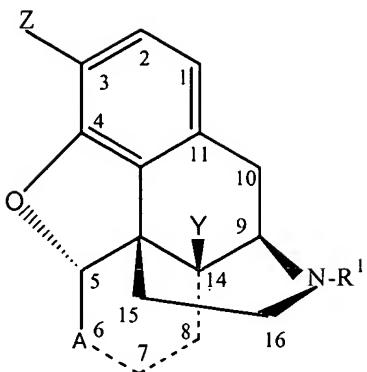
R¹ is hydrocarbyl or substituted hydrocarbyl,

R² is hydrocarbyl or substituted hydrocarbyl,

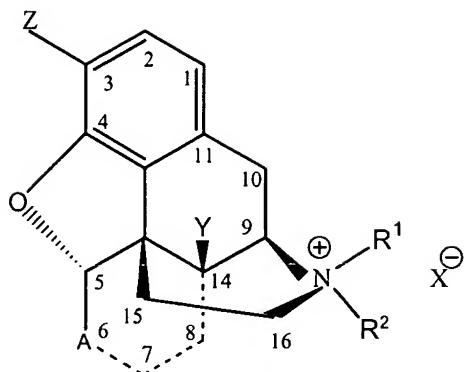
X⁻ is an anion, and

Z is hydroxy, alkoxy, or acyloxy.

80. (New) A process for the preparation of a quaternary derivative of a tertiary N-substituted morphinan alkaloid, the process comprising contacting a tertiary N-substituted morphinan alkaloid substrate with methyl bromide in an anhydrous solvent system, wherein the solvent system comprises an aprotic dipolar solvent selected from the group consisting of dimethylacetamide, dimethylformamide, 1-methyl-2-pyrrolidinone, hexamethylphosphoramide, and mixtures thereof with the aprotic dipolar solvent constituting at least 25 wt % of the solvent system, the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative have the structures of Formulae 1 and 1A, respectively:



Formula 1



Formula 1A

A is $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{=CH}_2)-$, $-\text{CH}(\text{A}_1)-$, or $-\text{C}(\text{A}_1)=$,

A_1 is hydroxy, alkoxy, or acyloxy,

each R is independently hydrocarbyl,

R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl,

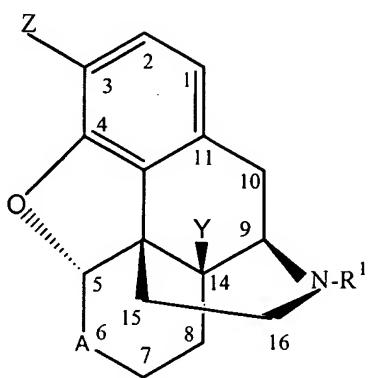
X^\ominus is an anion,

Y, if present, is hydrogen, hydroxy, alkoxy, acyloxy, $-\text{OTHP}$, $-\text{OSiR}_3$, $-\text{OBn}$, $-\text{OBs}$, $-\text{OTs}$, or $-\text{OMs}$,

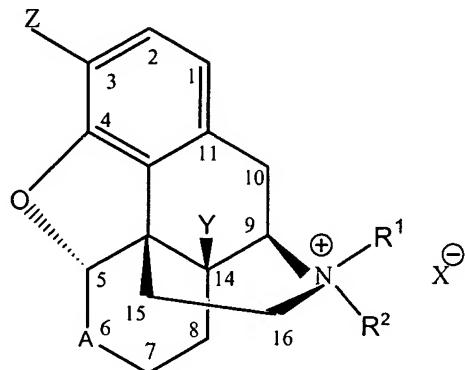
Z is hydroxy, alkoxy, acyloxy, $-\text{OTHP}$, $-\text{OSiR}_3$, $-\text{OBn}$, $-\text{OBs}$, $-\text{OTs}$, or $-\text{OMs}$, and

the dashed lines between the carbon atoms at positions 6 and 7, 7 and 8, and 8 and 14, respectively, represent (i) carbon-carbon single bonds, (ii) carbon-carbon single bonds between positions 6 and 7 and between positions 8 and 14, and a double bond between positions 7 and 8, or (iii) conjugated carbon-carbon double bonds between positions 6 and 7 and positions 8 and 14, with the proviso that Y is not present if there is a double bond between the carbons at positions 8 and 14.

81. (New) The process of claim 80 wherein the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 2 and 2A, respectively:



Formula 2



Formula 2A

A is $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{=CH}_2)-$, or $-\text{CH}(\text{A}_1)-$,

A_1 is hydroxy, alkoxy, or acyloxy,

R^1 is hydrocarbyl or substituted hydrocarbyl,

R^2 is hydrocarbyl or substituted hydrocarbyl,

X^\ominus is an anion,

Y is hydrogen, hydroxy, alkoxy, or acyloxy, and

Z is hydroxy, alkoxy, or acyloxy.

82. (New) The process of claim 81 wherein the tertiary N-substituted morphinan alkaloid substrate is naltrexone ((5 α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one), oxymorphone ((5 α)-4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one), oxycodone ((5 α)-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one), hydromorphone ((5 α)-4,5-epoxy-3-hydroxy-17-methylmorphinan-6-one), naloxone ((5 α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one), nalmefene ((5 α)-17-(cyclopropylmethyl)-4,5-epoxy-6-

methylenemorphinan-3,14-diol) or nalbuphine ((5 α)-17-(cyclobutylmethyl)-4,5-epoxymorphinan-3,6,14-triol).

83. (New) The process according to claim 80 wherein said process is carried out at a pressure of less than 1.25 atmospheres.

84. (New) The process according to claim 80 wherein the aprotic dipolar solvent constitutes at least 75 wt. % of the solvent system.

85. (New) The process according to claim 80 wherein said aprotic dipolar solvent is 1-methyl-2-pyrrolidinone.

86. (New) The process according to claim 80 wherein Y and Z are independently -OCH₃, -OAc, -OTHP, -OSiR₃, -OBn, -OBz, -OBs, -OTs, or -OMs wherein each R is independently hydrocarbyl.

87. (New) The process according to claim 80 wherein said anhydrous solvent system contains less than 0.2 wt. % water and is maintained in a moisture-free atmosphere in a reaction vessel.

88. (New) The process according to claim 80 wherein said anhydrous solvent system contains less than 0.1 wt. % water.

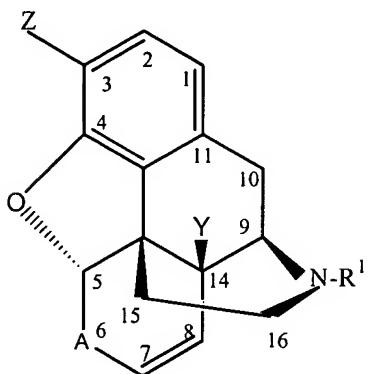
89. (New) The process according to claim 80 wherein said anhydrous solvent system contains less than 0.05 wt. % water.

90. (New) The process according to claim 89 wherein said methyl bromide and said substrate are present in a mole ratio of between 1:1 and 1.5:1, respectively.

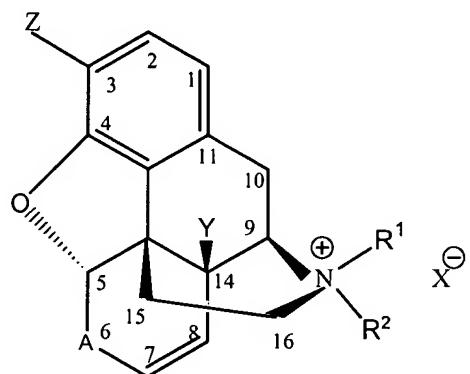
91. (New) The process according to claim 80 wherein said anhydrous solvent system and said substrate are present in a volume-to-weight ratio of 1.5:1-1.75:1.

92. (New) The process according to claim 80 wherein said contacting is carried out within a temperature range of about 55°C to about 85°C.

93. (New) The process of claim 80 wherein the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 3 and 3A, respectively:



Formula 3



Formula 3A

A is -C(O)-, -C(S)-, -C(=CH₂)-, or -CH(A₁)-,

A₁ is hydroxy, alkoxy, or acyloxy,

R¹ is hydrocarbyl or substituted hydrocarbyl,

R² is hydrocarbyl or substituted hydrocarbyl,

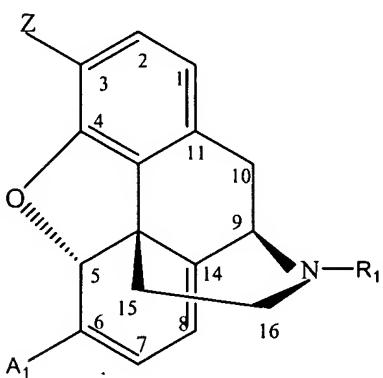
X⁻ is an anion,

Y is hydrogen, hydroxy, alkoxy, or acyloxy, and

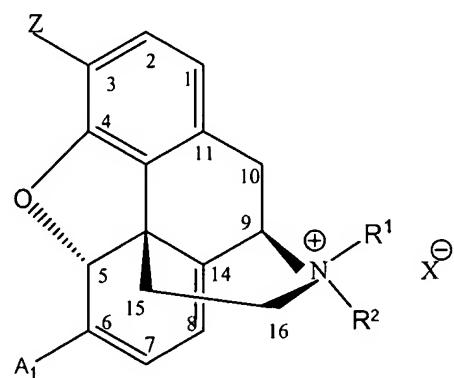
Z is hydroxy, alkoxy, or acyloxy.

94. (New) The process of claim 93 wherein the tertiary N-substituted morphinan alkaloid substrate is morphine ((5 α ,6 α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol), codeine ((5 α ,6 α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol), codeinone ((5 α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-one) or 14-hydroxy-codeinone ((5 α)-7,8-didehydro-4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one).

95. (New) The process of claim 80 wherein the tertiary N-substituted morphinan alkaloid substrate and the quaternary derivative correspond to Formulae 4 and 4A, respectively:



Formula 4



Formula 4A

A₁ is hydroxy, alkoxy, or acyloxy,

R¹ is hydrocarbyl or substituted hydrocarbyl,

R² is hydrocarbyl or substituted hydrocarbyl,

X⁻ is an anion, and

Z is hydroxy, alkoxy, or acyloxy.